

Application No. 10/088,354
Amendment Dated 08/12/2005
Reply to Office Action of 03/14/2005

Remarks/Arguments:

Claims 1-12, 15 and 16 were pending in the application. Contrary to the Office Action Summary, Claims 13 and 14 had been cancelled in Applicants response dated March 21, 2002 - they were not still pending as indicated in the Office Action.

Claims 11, 12, 15 and 16 remain pending in the application. Claims 1-10 have been cancelled. Claims 11, 12, 15 and 16 have been amended as described below. Claims 17-21 have been added.

In response to the Office Action:

- Claims 1-10 have been cancelled.
- Claim 11 has been amended to remove the un-elected subject matter by restricting it to a compound of formula IB. Parentheses have been removed and references to terms such as "hydrocarbonyl" have been replaced by more specific definitions as outlined herein below. The definitions of R¹ and R⁴ have been replaced with those found on page 18, lines 19-20 of the published PCT application. References to "amide" and "ester" have also been removed.
- Claim 12 has been amended to correct the dependencies and remove the non elected subject matter.
- Claim 15 has been amended to remove the non-elected subject matter and the references to "amide" and "ester".
- Portions of Claim 16 have been deleted to avoid repetition and the narrower definition of R⁶⁷ has been removed.
- Claims 17-21 have been added. Claims 17-20 are directed towards particular embodiments of the invention, Claim 21 is a method of treatment claim. Basis for these claims can be found in the specification, for example:
 - Claim 17 – page 32 line 15;
 - Claim 18 – page 26 line 30-32;
 - Claim 19 – page 27 line 1;
 - Claim 20 – page 27 line 2-5; and
 - Claim 21 – page 36 line 14-19.

Applicants have added a paragraph on page 1 after the title, to acknowledge the priority claim.

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Restriction Requirement

Applicants acknowledge that the restriction requirement has been made final. Claims 7-10 have been cancelled and the remaining claims amended in view of the restriction in order to further prosecution.

Claim Objections

1. Claims 5, 6 and 12 were objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to preceding claims in the alternative language. Claims 5 and 6 have been cancelled. Claim 12 has been amended to depend solely from claim 11. Applicants believe that these amendments overcome this objection.

Claim Rejections - 35 USC §112

Claims 1-4, 11, 15 and 16 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2a. Claim 1 recited the limitation of a "method for inhibiting aurora 2 kinase" which the Examiner alleged had indefinite metes and bounds because it is unclear what diseases are treated. Claim 1 has been cancelled rendering this objection moot.

2b. Claim 1 recited the limitation of "optionally substituted hydrocarbyl group" (e.g. definitions of R⁶ and R⁹) which the Examiner alleged had indefinite metes and bounds because a substituted hydrocarbyl group included an infinite number of combinations of a hydrocarbyl group with an unlimited number of functional groups and/or rings. Claim 1 has been cancelled rendering this objection moot. However the term "optionally substituted hydrocarbyl or optionally substituted heterocyclyl" also appeared in the definition of R⁹ in claim 11. This term has been replaced with the definition taken from page 19 line 14-18 of the published PCT application. Additionally, similar terms have been removed from the definition of R¹⁴ within the definition of R⁶⁶ and from the definition of R⁶⁷. The definition of R¹⁴ has been replaced with the definition from page 31 line 8 to page 32 line 2. This has been restricted to the definitions of group (1) and (10). The definitions of groups (1) and (10) have been incorporated into the claim from page 9 (for group (1)) and page 11 line 11 (for group (10)). Within group (10) the definition of R³⁸ came from page 10 line 28 to page 11 line 10 of the published PCT application and the definition of R⁹ came from page 13 line 4-6. Applicants believe that they have overcome this rejection.

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2c. Claims 1 and 11 recited the phrase "(other than ethenyl substituted by a carboxy group or an amide or sulphonamide derivative thereof)". The Examiner stated it was unclear if said phrase was a proviso, or if said phrase was meant to define the "substituted hydrocarbyl group" as being more than a substituted ethenyl group. Applicants have cancelled claim 1 and after applying the restriction requirement to claim 11, claim 11 no longer contains this phrase. Applicants believe that they have overcome this rejection.

2d. Claims 1, 11, 15 and 16 recited the limitation of "ester, amide or prodrug thereof which the Examiner stated rendered said claims indefinite because "ester, amide" are narrow limitations while "prodrug" is a broad limitation, and thus it was unclear which set of limitations were intended. The words "ester" and "amide" have been removed from claims 11, 15 and 16 to overcome this objection. Claim 1 has been cancelled.

2e. Claims 1-4, 11 and 16 recited limitations within parentheses (e.g. "(wherein...)" or "(linked via...)", etc.) and the Examiner stated it was unclear whether said limitations were part of the claims, or merely serve as examples. The objected to parentheses have been deleted.

2f. The Examiner stated that the proviso in claim 16 made the definition of R^{67} unclear since by the proviso, the alkoxy group represented by R^{67} must always be substituted, and not optionally substituted as stated at the beginning of the definition for R^{67} . Claim 16, in its amended form, does not contain this proviso. However this proviso also appeared in claim 11. The proviso has been deleted and as a consequence the word "optionally" has been deleted from the definition of R^{67} in claim 11. R^{67} is now C_1-6 alkoxy which is always substituted with a group X^1R^{38} (which cannot be hydrogen).

Claim Rejections - 35 USC §112

3. Claims 1-4 were rejected under 35 U.S.C. 112, first paragraph, because the Examiner said the specification, while being enabling for the treatment of colorectal cancer, did not reasonably provide enablement for the treatment of other diseases. Claims 1-4 have been cancelled rendering this objection moot.

Claim Rejections - 35 USC §103

Applicant confirms that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made.

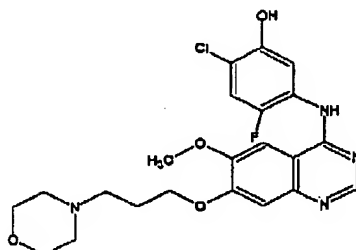
The Examiner alleges that claims 11, 15 and 16 are unpatentable over Thomas *et. al.* because, the Examiner alleges, Example 17, when combined with the generic teaching therein, would

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have motivated the skilled person to make a positional isomer of Example 17 with the hydroxy group at the para position on the phenyl ring with the expectation that such an isomer would have VEGF inhibitory activity.

Applicants respectfully disagree with the Examiner's conclusion.

The critical difference between Example 17 of Thomas *et. al.* which has the following structure:



and the present application is the presence of a $^{\text{a}}\text{-Z-(CH}_2\text{)}_n\text{-R}^{\text{a}}$ group in the position para to the X group of formula IIB of the present application. This group, as claimed, may not be halo. This group may be hydroxy, but is only present at the para position of the phenyl ring. R^{a} and R^{b} , the other substituents on the phenyl ring of formula IIB, may be halo, but not hydroxy.

In Example 17 of Thomas *et. al.*, the hydroxy group is in the meta position.

Applicants submit that Thomas *et. al.* provides no motivation to move the hydroxy group to the para position. Of the compounds bearing a hydroxy group that are specifically disclosed in Thomas *et al.*, all bear the hydroxy group at the meta position. None of the compounds have a hydroxy group at any other position.

In addition, column 4 lines 6-15 of Thomas *et. al.* (US'225) show preferred values and orientations of the groups attached to the phenyl ring. At line 21, R^{b} , the para substituent, is "hydrogen, methyl, methoxy, bromo, fluoro or chloro". No mention of hydroxy. At line 23, R^{c} , the meta substituent is described as "hydrogen or hydroxy, especially hydroxy". This is clearly providing direction to the skilled person, that where a hydroxy group is present it should be in the meta position.

In the alternative aspect of the invention given at column 4, line 26-31, hydroxy isn't the most preferred substituent for a substituent on the phenyl ring.

The teaching of Thomas *et. al.* with respect to hydroxy groups on the phenyl ring is therefore that they are not the most preferred substituent, and where they are present they should be in the meta position of the ring. There is no motivation provided by Thomas *et. al.* for the skilled

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person to make compounds that have a hydroxy group in the para position of the phenyl ring and arrive at the teaching of the present invention, only with a significant degree of hindsight could this conclusion be reached.

To further support this argument, Applicants respectfully remind the Examiner that the Examiner has selected 1 compound from a list of 36 compounds upon which to base the obviousness attack. There is nothing in this patent that would cause the skilled person to consider this particular compound over any other so the selection of this compound must have been made with the knowledge of our invention in mind.

Since Thomas *et. al.* provides that skilled person with no incentive to make compounds falling within the scope of claim 11, Applicants believe this claim, and consequently claims 15, 16 and newly added claims 17-21 are also patentable over Thomas *et. al.* and respectfully request that the Examiner acknowledges this fact.

The above amendments have been made without prejudice to Applicants right to prosecute any cancelled subject matter in a timely filed continuation application.

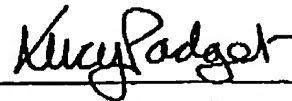
Applicants believe the application is in condition for allowance, which action is respectfully requested.

A petition for a 2 month extension of time is being filed herewith, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. Z70601-1P US.

Although Applicants believe no excess claim fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. Z70601-1P US.

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Enclosures: Transmittal Form
Fee Transmittal Form
Petition for Extension of Time